Agency for Healthcare Research and Quality
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NATIONAL GUIDELINE CLEARINGHOUSE

General

Guideline Title

Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for *CYP2C19* and voriconazole therapy.

Bibliographic Source(s)

Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, AgÃºndez JAG, Wingard JR, McLeod HL, Klein TE, Cross SJ, Caudle KE, Walsh TJ. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 and voriconazole therapy. Clin Pharmacol Ther. 2017 Jul;102(1):45-51. [40 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

NEATS Assessment

National Guideline Clearinghouse (NGC) has assessed this guideline's adherence to standards of trustworthiness, derived from the Institute of Medicine's report Clinical Practice Guidelines We Can Trust.

= Poor = Fair = Good = Very Good = Excellent

Assessment	Standard of Trustworthiness
YES	Disclosure of Guideline Funding Source
	Disclosure and Management of Financial Conflict of Interests
	Guideline Development Group Composition
YES	Multidisciplinary Group

UNKNOWN	Methodologist Involvement
▮▯▯▯▯	Patient and Public Perspectives
	Use of a Systematic Review of Evidence
▮▮▮▮▯	Search Strategy
▮▮▮▮▯	Study Selection
▮▮▮▯▯	Synthesis of Evidence
	Evidence Foundations for and Rating Strength of Recommendations
▮▮▮▮▯	Grading the Quality or Strength of Evidence
▮▮▮▮▮	Benefits and Harms of Recommendations
▮▮▮▯▯	Evidence Summary Supporting Recommendations
▮▮▮▮▮	Rating the Strength of Recommendations
▮▮▮▮▮	Specific and Unambiguous Articulation of Recommendations
▮▮▯▯▯	External Review
▮▮▮▮▯	Updating

Recommendations

Major Recommendations

The strength of therapeutic recommendations (Strong, Moderate, Optional) is defined at the end of the "Major Recommendations" field.

Genetic Test Interpretation

Each named star (*) allele is defined by the genotype of one or more specific variants, some of which are associated with a level of enzyme activity (see *CYP2C19* allele definition table [see the "Availability of Companion Documents" field]). Table 1, below, summarizes the assignment of the likely cytochrome P450 2C19 (CYP2C19) metabolizer phenotypes based on *CYP2C19* star (*) allele diplotypes and these assignments are used to guide the *CYP2C19*-directed voriconazole treatment recommendations (see Tables 2 and 3, below).

Previously published Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for clopidogrel and tricyclic antidepressants define CYP2C19 ultrarapid metabolizers as individuals who carry one *CYP2C19*17* allele in combination with a normal function *CYP2C19*1* allele or who are *CYP2C19*17* homozygous. This definition was based on pharmacokinetic data that analyze *CYP2C19*17* carriers *(*1/*17* and *17/*17*) from noncarriers of *CYP2C19*17* (*CYP2C19*1/*1*) separately. This guideline introduces the term "CYP2C19 rapid metabolizer" to define those who carry one *CYP2C19*17* allele in combination with a normal function *CYP2C19*1* allele. Statistical differences in mean pharmacokinetic parameters between *CYP2C19*1/*17* and *CYP2C19*1/*1* has been observed, but the range of

pharmacokinetic parameters often overlaps. Whether this definition of rapid metabolizer is appropriate for all CYP2C19 substrates is unclear and may depend on the impact of other metabolic pathways involved in the metabolism of each drug. As this distinction may be drug dependent, introducing the term "rapid metabolizer" allows for a distinctive recommendation between these phenotype groups when needed. Of note, the limited data available distinguishing rapid (**1/*17*) and ultrarapid (**17/*17*) *CYP2C19* metabolizers treated with voriconazole prompted similar recommendations for these two CYP2C19 metabolizer phenotypes in adults. However, for children, as there is insufficient evidence to distinguish a *CYP2C19*1/*17* and *CP2C19*1/*1* pediatric patient due to large variability in trough concentrations, there are separate recommendations for CYP2C19 ultrarapid and rapid metabolizers.

Available Genetic Test Options

Commercially available genetic testing options change over time. Additional information about pharmacogenetic testing can be found at the Genetic Testing Registry (http://www.ncbi.nlm.nih.gov/gtr/).

Incidental Findings

Variant *CYP2C19* alleles have been associated with the development of voriconazole-associated squamous cell carcinoma; however, this study has not been adequately replicated at this time to warrant any clinical action. CYP2C19 is directly involved in the metabolism of proton pump inhibitors, and variant *CYP2C19* alleles have been implicated in the development and progression of gastritis, peptic ulcer disease, and gastric carcinoma. In addition, no function *CYP2C19* alleles have reproducibly been associated with lower active metabolite levels of clopidogrel, decreased metabolism of metamizole, decreased platelet inhibition, and increased adverse cardiovascular event rates among patients with clopidogrel-treated acute coronary syndrome undergoing percutaneous coronary intervention. CYP2C19 and CYP2D6 are involved in the metabolism of tricyclic antidepressants and selective serotonin reuptake inhibitors, and the available evidence supporting an association between variant alleles and antidepressant response prompted *CYP2C19* and *CYP2D6* genotype-directed CPIC guidelines for these medications.

Table 1. Assignment of Likely CYP2C19 Phenotypes Based on Genotypes

Likely Phenotype	**Genotypes[a]**	**Examples of *CYP2C19* Diplotypes**
CYP2C19 ultrarapid metabolizer (~2%-5% of patients)[b]	An individual carrying two increased function alleles	**17/*17*
CYP2C19 rapid metabolizer (~2%-30% of patients)[b]	An individual carrying one normal function allele and one increased function allele	**1/*17*
CYP2C19 normal metabolizer (~35%-50% of patients)[b]	An individual carrying two normal function alleles	**1/*1*
CYP2C19 intermediate metabolizer (~18%-45% of patients)[b]	An individual carrying one normal function allele and one no function allele or one no function allele and one increased function allele	**1/*2, *1/*3, *2/*17*[d]
CYP2C19 poor metabolizer (~2%-15% of patients)[b]	An individual carrying two no function alleles	**2/*2, *2/*3, *3/*3*

[a]Assignment of allele function (CYP2C19 allele definition table [see the "Availability of Companion Documents" field]) and citations for allele function (CYP2C19 allele functionality references) are posted to PharmGKB.org.

[b]See the CYP2C19 frequency table (see the "Availability of Companion Documents" field) for race specific allele and phenotype frequencies.

[c]Based on the CPIC term standardization project (reference in press), the term "normal metabolizer" will be used instead of the term

"extensive metabolizer" in all new and updated CPIC guidelines.

[d]The predicted metabolizer phenotype for the *2/*17 genotypes is a provisional classification. The currently available evidence indicates that the *CYP2C19*17* increased function allele is unable to completely compensate for the no function *CYP2C19*2*.

See Supplemental Materials (see the "Availability of Companion Documents" field) for a more comprehensive list of predicted metabolizer phenotypes.

Therapeutic Recommendation

Clinical studies have not consistently demonstrated an association between *CYP2C19* genotype and adverse reactions. However, as individual patients who are poor metabolizers may have elevated levels leading to toxicity, the use of another antifungal agent is recommended. Under circumstances in which voriconazole is strongly indicated for treatment of an invasive mycosis in a patient with a poor metabolizer phenotype, administration of a lower dosage with meticulous therapeutic drug monitoring (TDM) may be feasible (see Tables 2 and 3, below).

Knowledge of CYP2C19 ultrarapid and rapid metabolizer genotypes may prevent subtherapeutic concentrations of voriconazole that may lead to treatment failure. In such cases, an alternative antifungal agent also is recommended, especially as several case reports have documented voriconazole treatment failure in CYP2C19 ultrarapid metabolizers (see Supplementary Table S1). Attempting to obtain therapeutic levels in patients with ultrarapid metabolizer genotypes are often unsuccessful. Serious delays in achieving therapeutic concentrations in such patients with active invasive mycoses may result in disease progression.

Several alternative agents may be used instead of voriconazole for treatment of invasive mold infections. These include isavuconazole, lipid formulations of amphotericin B, and posaconazole (see Tables 2 and 3, below). The antifungal triazole isavuconazole is approved for the primary treatment of invasive aspergillosis and invasive mucormycosis and is available in intravenous and oral dosage forms. As isavuconazole is a substrate of CYP3A4, variant alleles in this gene are unlikely to affect its clearance. Only limited data for isavuconazole are currently available in the pediatric population. Liposomal amphotericin B is an alternative therapy to voriconazole for the primary treatment of invasive aspergillosis. Posaconazole is currently indicated for salvage therapy of invasive aspergillosis. The recently approved posaconazole delayed release and intravenous dosage forms achieve higher concentrations than that of the posaconazole suspension. However, intravenous posaconazole requires administration via a central line due to phlebitis with peripheral administration. Similar to voriconazole, intravenous posaconazole also contains the solubilizer sulfobutylether-beta-cyclodextrin sodium. Posaconazole is cleared largely as unchanged compound with <20% of compound being excreted as a glucuronide conjugate. Uridine 5'-diphosphoglucuronosyltransferase glucuronidation of posaconazole is not significantly affected by genetic variation. Administration of posaconazole should still be guided by TDM.

Other Considerations

Further dose adjustments of voriconazole or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, fungal species, TDM, comorbidities, and site of infection. Assessment of drug interactions with a patient's concomitant medications is important before initiating voriconazole. Voriconazole is a potent CYP450 enzyme inhibitor and interacts with numerous medications, including calcineurin inhibitors, sirolimus, vinca alkaloids, cyclophosphamide, and HMG-CoA reductase inhibitors. By comparison, CYP2C19 inhibitors, such as omeprazole and cimetidine, may lead to increased voriconazole concentrations. CYP3A4 inhibitors may increase voriconazole concentrations in patients who are CYP2C19 poor metabolizers. Furthermore, concomitant use of CYP450 enzyme inducers may lead to subtherapeutic voriconazole concentrations and clinical failure. In patients with mild to moderate hepatic impairment, a dose adjustment for voriconazole is recommended. However, selection of an alternative antifungal agent may be reasonable in patients with significant hepatic impairment due to the risk of voriconazole hepatotoxicity. In patients with renal failure, the solubilizer of intravenous voriconazole (sulfobutylether-beta-cyclodextrin sodium) may accumulate. Although the manufacturer suggests using oral voriconazole in patients with creatinine clearance <50 mL/min unless the benefits outweigh the risk, there seems to be no deleterious effect of the sulfobutylether-beta-

cyclodextrin in this patient population receiving the parenteral formulation. The availability and turnaround time of voriconazole concentrations at an institution may affect the ability to perform voriconazole TDM. Finally, comorbid conditions, such as obesity, may require using an adjusted body weight instead of total body weight when using weight-based dosing of voriconazole.

Genetic variation in *CYP3A4*, *CYP3A5*, and *CYP2C9* seems not to significantly affect the pharmacokinetics of voriconazole. In an analysis of the placebo groups of two drug interaction studies in healthy volunteers, *CYP3A5* variants did not affect the pharmacokinetics of voriconazole. The lack of association of *CYP3A5* and voriconazole pharmacokinetics was also observed in a single and multiple dose voriconazole study in healthy volunteers. Furthermore, the pharmacokinetic parameters of voriconazole in a CYP2C19 normal metabolizer patient with a *CYP2C9*2/*2* genotype were similar when compared with patients with a *CYP2C9*1/*1* genotype.

Table 2. Dosing Recommendations for Voriconazole Treatment Based on CYP2C19 Phenotype for Adult Patients

Phenotype	Implications for Voriconazole Pharmacologic Measures	Therapeutic Recommendations	Classification of Recommendations
CYP2C19 ultrarapid metabolizer (**17/*17*)	In patients for whom an ultrarapid metabolizer genotype (**17/*17*) is identified, the probability of attainment of therapeutic voriconazole concentrations is small with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[a]	Moderate[b]
CYP2C19 rapid metabolizer (**1/*17*)	In patients for whom a rapid metabolizer genotype (**1/*17*) is identified, the probability of attainment of therapeutic concentrations is moderate with standard dosing	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[a]	Moderate
CYP2C19 normal metabolizer	Normal voriconazole metabolism	Initiate therapy with standard care of dosing[a]	Strong
CYP2C19 intermediate metabolizer	Higher dose-adjusted trough concentrations of voriconazole compared with normal metabolizers	Initiate therapy with standard care of dosing[a]	Moderate
CYP2C19 poor metabolizer	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include isavuconazole, liposomal amphotericin B, and posaconazole.[a] In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than	Moderate

Phenotype	Implications for Voriconazole Pharmacologic Measures	Therapeutic Recommendations	Classification of Recommendations
		standard dosage with careful therapeutic drug monitoring.	

[a]Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, therapeutic drug monitoring, and comorbidities.

[b]Recommendations based upon data extrapolated from patients with *CYP2C19*1/*17* genotype.

Table 3. Dosing Recommendations for Voriconazole Treatment Based on CYP2C19 Phenotype for Pediatric Patients (Children and Adolescents <18 Years Old)

CYP2C19 Phenotype	Implications for Voriconazole Pharmacologic Measures	Therapeutic Recommendations	Classification of Recommendations
CYP2C19 ultrarapid metabolizer (**17/*17*)	In patients for whom an ultrarapid metabolizer genotype (**17/*17*) is identified, the probability of attainment of therapeutic voriconazole concentrations is small	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include liposomal amphotericin B and posaconazole.[a,b]	Moderate
CYP2C19 rapid metabolizer (**1/*17*)	In patients for whom a rapid metabolizer genotype (**1/*17*) is identified, the probability of attainment of therapeutic concentrations is variable	Initiate therapy with standard care of dosing.[a] Use therapeutic drug monitoring to titrate dose to therapeutic trough concentrations.[b,c]	Moderate
CYP2C19 normal metabolizer	Normal voriconazole metabolism	Initiate therapy with standard care of dosing[c]	Strong
CYP2C19 intermediate metabolizer	Higher dose-adjusted trough concentrations of voriconazole compared with normal metabolizers	Initiate therapy with standard care of dosing[c]	Moderate
CYP2C19 poor metabolizer	Higher dose-adjusted trough concentrations of voriconazole and may increase probability of adverse events	Choose an alternative agent that is not dependent on CYP2C19 metabolism as primary therapy in lieu of voriconazole. Such agents include liposomal amphotericin B and posaconazole.[a,d] In the event that voriconazole is considered to be the most appropriate agent, based on clinical advice, for a patient with poor metabolizer genotype, voriconazole should be administered at a preferably lower than standard dosage with careful therapeutic drug monitoring.	Moderate[d]

[a]Further dose adjustments or selection of alternative therapy may be necessary due to other clinical factors, such as drug interactions, hepatic function, renal function, species, site of infection, therapeutic drug monitoring, and comorbidities.

[b]Achieving voriconazole therapeutic concentrations in the pediatric population with ultrarapid and rapid metabolizer phenotypes in a timely

manner is difficult. As critical time may be lost in achieving therapeutic concentrations, an alternative antifungal agent is recommended in order that the child receives effective antifungal therapy as soon as possible.

[c]Meticulous TDM is critical for rapid metabolizers. There is insufficient evidence to distinguish a *CYP2C19*1/*17* and **1/*1* pediatric patient due to large variability in trough concentrations.

[d]Recommendation based upon data extrapolated from adults.

Definitions

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Fungal infection, including invasive aspergillosis, candidemia in non-neutropenic patients, disseminated *Candida* infections, esophageal candidiasis, as well as infections caused by *Scedosporium apiospermum* and *Fusarium* species

Guideline Category

Evaluation

Risk Assessment

Treatment

Clinical Specialty

Family Practice

Infectious Diseases

Medical Genetics

Pediatrics

Pharmacology

Intended Users

Advanced Practice Nurses

Pharmacists

Physician Assistants

Physicians

Guideline Objective(s)

To provide information that allows evidence-based interpretation of clinical cytochrome P450 (*CYP2C19*) genotype test results in order to guide dosing of voriconazole or selection of an alternative antifungal agent for treatment that is not significantly metabolized predominantly by *CYP2C19*

Target Population

Patients being treated for invasive fungal infections

Interventions and Practices Considered

Use of cytochrome P450 2C19 (*CYP2C19*) genotyping to guide therapeutic decision-making and dosing of voriconazole

Major Outcomes Considered

Effect of cytochrome P450 2C19 (*CYP2C19*) on voriconazole clinical outcomes or effect on voriconazole pharmacokinetic parameters

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Retrieval of the Evidence Linking Genotype to Drug Variability

The PharmGKB Scientific Curator, the Clinical Pharmacogenetics Implementation Consortium (CPIC) coordinator or authors with experience in literature or systematic review conduct the literature review and present the results to the writing committee. A search of PubMed and OVID MEDLINE is performed using the keywords for the gene and drug of interest, for example: (gene name) OR (gene symbol) OR (dbSNP rs number) OR (gene common names) AND (drug name OR drug class name). Furthermore, papers listed on PharmGKB are cross-checked as there may be annotations for the papers and/or additional publications. Where available, evidence evaluating the outcomes when prescribing has been altered based on genetic testing is included. For most gene-drug pairs, randomized controlled trials comparing clinical outcomes with genotype-guided dosing versus conventional dosing are not available.

Literature Review

The authors searched the PubMed® database (1966 to May 2016) for the following keywords: (cytochrome P450 2C19 or CYP2C19) AND (voriconazole). Using these search terms, 134 publications were identified. In addition, studies annotated in PharmGKB (http://www.pharmgkb.org) were identified. Study inclusion criteria included publications that included analyses for the association between *CYP2C19* genotypes and metabolism of voriconazole or voriconazole-related adverse drug events or clinical outcomes. Non-English manuscripts were excluded.

The *CYP2C19* frequency table includes updates of those previously published in CPIC guidelines. Updates to the *CYP2C19* frequency tables were made by searching the PubMed® database (1995 to 2015). The following criteria were used for *CYP2C19*: (CYP2C19 or 2C19 or cytochrome P4502C19) AND (genotype OR allele OR frequency OR minor allele OR variant OR ethnic OR race OR racial OR ethnicity) with filter limits set to retrieve "full-text" and "English" literature. In addition, reports were also identified from citations by others or review articles. Studies were considered for inclusion in the *CYP2C19* frequency table if: (1) the ethnicity of the population was clearly indicated, (2) either allele frequencies or genotype frequencies were reported, (3) the method by which the genes were genotyped was indicated, (4) the sample population consisted of at least 50 individuals with a few exceptions (e.g., smaller cohorts that were part of larger studies) and (5) the study represented an original publication (no reviews or meta-analyses). Diplotype and phenotype frequencies were estimated using the equation describing Hardy Weinberg equilibrium based on reported allele frequencies.

Number of Source Documents

Following application of the inclusion criteria, 35 publications were reviewed and included in the evidence table (see Supplemental Table S1 [see the "Availability of Companion Documents" field).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Levels of Evidence Linking Genotype to Phenotype

High: Evidence includes consistent results from well-designed, well-conducted studies.

Moderate: Evidence is sufficient to determine effects, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies; generalizability to routine practice; or indirect nature of the evidence.

Weak: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information.

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Some of the factors that are taken into account in evaluating the evidence supporting therapeutic recommendations include: *in vivo* pharmacokinetic and pharmacodynamic data, in vitro enzyme activity of tissues expressing wild-type or variant-containing CYP2C19, *in vitro* CYP2C19 enzyme activity from tissues isolated from individuals of known *CYP2C19* genotypes, and *in vivo* pre-clinical and clinical pharmacokinetic and pharmacodynamic studies. The gene-based dosing recommendations in this guideline take into consideration the effects *CYP2C19* genetic variants may have on both clinical outcomes and voriconazole pharmacokinetics.

Summarization and Presentation of the Evidence Linking Genotype to Drug Variability

Publications supporting a major finding are usually considered as a group and scored by members of the writing committee based on the totality of the evidence supporting that major finding. Thus, it is possible for an evidentiary conclusion based on many papers, each of which may be relatively weak, to be graded as "moderate" or even "strong," if there are multiple small case reports or studies that are all supportive with no contradictory studies. The rating scheme (see the "Rating Scheme for the Strength of the Evidence" field) uses a scale modified slightly from Valdes et al. Primary publications are summarized in the Evidence Table which is published in the manuscript supplemental material (see the "Availability of Companion Documents" field). It is the writing committee's evaluation of this evidence that provides the basis for the therapeutic recommendation(s).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Identification of Content Experts and Formation of Writing Committee

Once a guideline topic has been approved by Clinical Pharmacogenetics Implementation Consortium (CPIC) members and the Steering Committee, a senior author is identified through self-nomination or by request of the CPIC Steering Committee. The senior author takes responsibility for forming the writing committee and completing the guideline. The writing committee is multidisciplinary, comprising a variety of scientists, pharmacologists, and clinicians (e.g., pharmacists and physicians). Authors will have a track record of publication and/or expertise in the specific topic area of the guideline. PharmGKB assigns at least one Scientific Curator to each CPIC guideline writing committee who has expertise in searching, compiling and evaluating the evidence for gene-drug associations, and making it computable and available on the PharmGKB Web site. Furthermore, PharmGKB curators often take primary responsibility for completing background gene and drug summaries, assigning likely phenotypes based on genotypes (i.e., "Table 1" in guidelines), literature review, as well as preparing supplementary material provided in each guideline (i.e., genotypes that constitute the star (*) alleles or haplotypes, frequencies of alleles in major race/ethnic groups, genetic test interpretation and availability, and evidence linking genotype with phenotype).

Development of Therapeutic Recommendation and Assignment of Strength of the Recommendation

The writing committee discusses the evaluation of the literature and develops a draft recommendation via Web conferences and email communication. CPIC's therapeutic recommendations are based on weighing the evidence summarized in the supplementary Evidence Table from a combination of preclinical functional and clinical data, as well as on any existing consensus guidelines. Evidence related to the suitability of alternative medications or dosing that may be used based on genetics must be weighed in assigning the strength of the recommendation. Overall, the therapeutic recommendations are simplified to allow rapid interpretation by clinicians and are presented in the Table 2 of each guideline and occasionally in an algorithm.

To assign strength to a recommendation, CPIC uses a transparent three category system (see the "Rating

Scheme for the Strength of the Recommendations" field) for rating recommendations that was adopted with slight modification from the rating scale for evidence-based recommendations on the use of antiretroviral agents (http://aidsinfo.nih.gov/contentfiles/AdultandAdolescentGL.pdf). Each recommendation also includes an assessment of its usefulness in pediatric patients.

CPIC guidelines currently focus on gene-drug pairs for which at least one of the prescribing recommendations is actionable (e.g., recommendation to alter a dose or consider an alternative drug based on the genotype-phenotype relationship). For these and many other gene-drug pairs, PharmGKB also contains clinical annotations that are genotype-based summaries of the association between a drug and a particular variant. Each clinical annotation is assigned a level of evidence depending on population, replication, effect size and statistical significance.

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for additional information.

Rating Scheme for the Strength of the Recommendations

Strength of Therapeutic Recommendations

Strong: The evidence is high quality and the desirable effects clearly outweigh the undesirable effects.

Moderate: There is a close or uncertain balance as to whether the evidence is high quality and the desirable clearly outweigh the undesirable effects.

Optional: The desirable effects are closely balanced with undesirable effects and there is room for differences of opinion as to the need for the recommended course of action.

No recommendation: There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time

Cost Analysis

Cost-effectiveness analyses of cytochrome P450 2C19 (*CYP2C19*) genotyping are beyond the scope of the guideline.

Method of Guideline Validation

External Peer Review

Internal Peer Review

Description of Method of Guideline Validation

Internal and External Review, Comment, and Approval Process

Once the writing committee has completed and approved a draft guideline, the draft guideline is circulated to the Clinical Pharmacogenetics Implementation Consortium (CPIC) co-leaders and coordinator for content review. The guideline is reviewed for compliance with the CPIC Standard Operating Procedures and required format. The guideline draft is then discussed on a CPIC conference call with all CPIC members and circulated to the members for further review and approval. At each stage, feedback is considered for incorporation into the guideline and/or revision of the guideline, as supported by the available evidence and expert clinical judgment of the senior author and writing committee. Finally, the guideline manuscript under goes typical external scientific peer review by the journal prior to publication.

Current agreements with the American Society for Clinical Pharmacology and Therapeutics give the journal *Clinical Pharmacology and Therapeutics* the first right of refusal for publication of CPIC guidelines; as part of this agreement, the guidelines are freely posted to PharmGKB immediately upon publication. In general *Clinical Pharmacology and Therapeutics* uses a minimum of two external expert peer-reviewers and an editorial board member with content expertise as reviewers for each CPIC guideline.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The evidence summarized in Supplemental Table S1 (see the "Availability of Companion Documents" field) is graded on a scale of high, moderate, and weak, based upon the level of evidence (see the "Rating Scheme for the Strength of the Evidence" field). Every effort was made to present evidence from high-quality studies.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Voriconazole dosing is routinely directed by therapeutic drug monitoring (TDM). However, for patients with available *CYP2C19* genotyping results, subtherapeutic and supratherapeutic voriconazole concentrations could be avoided by choosing alternative agents in ultrarapid/rapid metabolizers and poor metabolizers, respectively.

Potential Harms

- Although *CYP2C19* genotyping is considered reliable when performed in qualified clinical laboratories, genotyping and/or human error is always a rare possibility. Prospectively collected data from studies seeking to establish and validate dosages in poor metabolizers are needed in order to provide additional options to clinicians caring for these patients.
- The adverse events of voriconazole include hepatotoxicity, neurotoxicity (visual hallucinations, encephalopathy, and neuropathy), photopsia, skin rash, photosensitivity, visual disturbances, and periostitis with or without hyperfluorosis. Adverse effects that have been correlated with voriconazole concentrations include hepatotoxicity, visual disturbances, visual hallucinations, and other neurologic disorders. In addition, a decreased clinical response has been reported with low voriconazole concentrations.

Qualifying Statements

Qualifying Statements

Caveats: Appropriate Use and/or Potential Misuse of Genetic Tests

CYP2C19 genotyping cannot replace therapeutic drug monitoring (TDM), as other factors (i.e., drug interactions, hepatic function, renal function, species, site of infection, and comorbidities) also influence the use of voriconazole. Rare *CYP2C19* variants are typically not included in common genotyping tests and patients are therefore assigned the "wild-type" (*CYP2C19*1*) allele by default. Thus, in rare cases, an

assigned "wild-type" allele may harbor a no, decreased, or increased function variant. An individual's predicted CYP2C19 metabolizer status may also depend on other factors, including epigenetic phenomena, diet, comorbidities, or co-medications.

Disclaimer

The Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines reflect expert consensus based on clinical evidence and peer-reviewed literature available at the time they are written, and are intended only to assist clinicians in decision-making, as well as to identify questions for further research. New evidence may have emerged since the time a guideline was submitted for publication. Guidelines are limited in scope and are not applicable to interventions or diseases not specifically identified. Guidelines do not account for all individual variations among patients and cannot be considered inclusive of all proper methods of care or exclusive of other treatments. It remains the responsibility of the healthcare provider to determine the best course of treatment for the patient. Adherence to any guideline is voluntary, with the ultimate determination regarding its application to be solely made by the clinician and the patient. The CPIC assumes no responsibility for any injury to persons or damage to property related to any use of CPIC's guidelines, or for any errors or omissions.

CPIC is a registered service mark of the United States Department of Health and Human Services (HHS).

Underlying Assumption

The key underlying assumption for all CPIC guidelines is that clinical high-throughput and pre-emptive genotyping will eventually become common practice and clinicians will increasingly have patients' genotypes available before a prescription is written. Therefore, CPIC guidelines are designed to provide guidance to clinicians as to how available genetic test results should be interpreted to ultimately improve drug therapy, rather than to provide guidance as to whether a genetic test should or should not be ordered.

Implementation of the Guideline

Description of Implementation Strategy

Implementation of This Guideline

The guideline supplement contains resources that can be used within electronic health records to assist clinicians in applying genetic information to patient care for the purpose of drug therapy optimization (see "Resources to incorporate pharmacogenetics into an electronic health record with clinical decision support" section of the Supplementary Materials [see the "Availability of Companion Documents" field).

Refer to "Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process" (see the "Availability of Companion Documents" field) for information on guideline dissemination and connecting the guidelines to practice.

Implementation Tools

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Moriyama B, Obeng AO, Barbarino J, Penzak SR, Henning SA, Scott SA, AgÃºndez JAG, Wingard JR, McLeod HL, Klein TE, Cross SJ, Caudle KE, Walsh TJ. Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines for CYP2C19 and voriconazole therapy. Clin Pharmacol Ther. 2017 Jul;102(1):45-51. [40 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2017 Jul

Guideline Developer(s)

Clinical Pharmacogenetics Implementation Consortium - Independent Expert Panel

Source(s) of Funding

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Financial Disclosures/Conflicts of Interest

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Management of Conflicts of Interest

All authors must declare any funding interests and activities potentially resulting in conflict of interest by written disclosure to the Clinical Pharmacogenetics Implementation Consortium (CPIC) Steering Committee and writing committee before the approval of the authorship plan. Included are all possible conflicts including spouses/family members in declarations, National Institutes of Health (NIH) funding that could be interpreted to indicate that authors are "advocates" of the recommendations, as well as any sources of revenue from consulting, patents, stock ownership, etc. All conflicts of interest are reported in the guideline manuscript.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) Web site.

Availability of Companion Documents

The following are available:

- Supplementary material, including tables and methodological information, is available from the Clinical Pharmacogenetics Implementation Consortium (CPIC) Web site.
- A variety of resources, including definition, frequency, functionality, and diplotype-phenotype tables; drug mapping; gene resource mapping; and clinical decision support, are available from the CPIC Web site.
- Caudle KE, Klein TE, Hoffman JM, et al. Incorporation of pharmacogenomics into routine clinical practice: the Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline development process. Curr Drug Metab. 2014;15(2):209-17. Available from the CPIC Web site.

Patient Resources

None available

NGC Status

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